NOVEL 1-AR(ALK)YLIMIDAZOLIN-2-ONES HAVING ANTICONVULSIVE ACTIVITY, WHICH CONTAIN A DISUBSTITUTED AMINE RADICAL IN THE 4-POSITION, AND PROCESSES FOR THEIR PREPARATION

The invention relates to 1-ar(alk)ylimidazolin-2-ones which contain a disubstituted amine radical in the 4-position, processes for their preparation and their use as pharmaceutical agents for the treatment of disorders of the central nervous system, in particular of epilepsies of various forms.

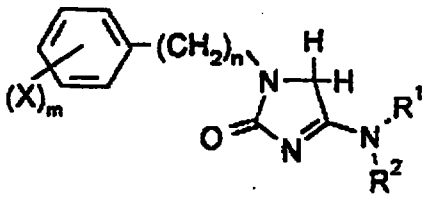
1-Ar(alk)ylimidazolin-2-ones having an unsubstituted amine or methylamine radical in the 4-position are prepared according to the prior art by reaction of ar-(alk)ylaminoacetamides with cyanogen bromide. By N-alkylation of the 4-amino-1-ar(alk)ylimidazolin-2-ones prepared in this way, 3-alkyl- or 1-iminoalkyl-3-alkyl-1-ar(alk)ylimidazolin-2-ones are obtained, the amino group in the 4-position being tautomerized to an imino group. A further N-alkylation to give compounds of the general formula **1** is therefore not possible, so that compounds according to the invention cannot be prepared by this process [USP 4044021; DE 2251354].

1-Ar(alk)ylimidazolin-2-ones having a disubstituted amine radical in the 4-position have not been described until now.

A multiplicity of compounds having anticonvulsive activity are known. However, even today not all epileptic disorders can be treated satisfactorily.

The invention is thus based on the object of making available novel compounds having favorable pharmacological properties which can be employed, for example, as medicaments having antiepileptic activity.

According to the present invention, these novel compounds are 1-ar(alk)ylimidazolin-2-ones of the general formula **1**



n = 0, 1
m = 0, 1, 2, 3, 4, 5

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in which

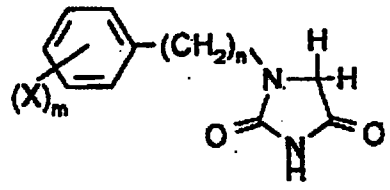
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl or halogen,
R^1 and R^2 = C_1-C_4-alkyl, cycloalkyl or heteroalkyl
or .
R^1 and R^2 together are an alkylene group having 2-6 carbon atoms in which a $-CH_2-$ group can be replaced by oxygen, nitrogen or sulfur.

The number of CH_2 groups is either 0 (1-arylimidazolin-2-ones) or 1 (1-aralkylimidazolin-2-ones).

Examples of compounds of the general formula **I** [sic] which may be mentioned are:

1-phenyl-4-morpholinoimidazolin-2-one
1-(4-methoxy)-4-piperidinoimidazolin-2-one
1-(4-chlorophenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-piperidinoimidazolin-2-one
1-(4-chlorophenyl)-4-dimethylaminoimidazolin-2-one
1-(4-bromophenyl)-4-morpholinoimidazolin-2-one
1-(3-chlorophenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-hexamethyleneiminoimidazolin-2-one
1-(4-chlorophenyl)-4-(4-methylpiperazino)imidazolin-2-one
1-(4-methylphenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-(cyclohexylmethylamino)imidazolin-2-one
1-(4-fluorophenyl)-4-morpholinoimidazolin-2-one
1-benzyl-4-morpholinoimidazolin-2-one

According to the present invention, the compounds of the general formula **1** can be prepared by a novel process by reaction of the compounds of the general formula **2**



n = 0, 1
m = 0, 1, 2, 3, 4, 5

in which

X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl or halogen,

with a secondary amine.

The preparation of the compounds of the formula **1** can alternatively be carried out in a solvent or in excess secondary amine at temperatures between 50°C and 160°C. Suitable solvents are preferably aromatic hydrocarbons, for example benzene, toluene, chlorobenzene or dichlorobenzene.
The reaction is preferably carried out in the presence of water-binding substances such as zeolites or sodium sulfate. The reaction can be accelerated by addition of generally customary condensation catalysts such as 4-toluenesulfonic acid.

The compounds according to the invention are suitable for the preparation of pharmaceutical compositions. The pharmaceutical compositions can contain one or more of the compounds according to the invention. The customary pharmaceutical excipients and auxiliaries can be used to prepare the pharmaceutical preparations.

The medicaments can be administered parenterally (for example intravenously, intramuscularly or subcutaneously) or orally.

The administration forms can be prepared by processes which are generally known and customary in pharmaceutical practice.

The compounds according to the invention have strong anticonvulsive actions.

They were tested for their anticonvulsive action in vivo after i.p. administration to mice or rats (p.o. administration) according to the internationally customary standard (Pharmac. Weekblad, Sc.Ed. **14**, 132 (1992) and Antiepileptic Drugs, Third Ed., Raven Press, New York (1989) (Table 1).

For example, for the compound 2 (1-(4-chlorophenyl)-4-morpholinoimidazolin-2-one) in the rat the ED_{50} (p.o.) for the maximum electroshock was determined to be 21 mg/kg, the ED_{50} in the s.c. pentetrazole test was determined to be 16 mg/kg and the NT_{50} for the neurotoxicity was determined to be > 400 mg/kg. In comparison to this, known antiepileptics are active either in the maximum electroshock model or in the pentetrazole test or, in the case of relatively high activity, are severely neurotoxic in the PTZ test.

Table 1

Compound according to Examples	Log P[2)]	Test[3)]	Dose[4)]	Action[5)]
1	0.64	MES	100	30
		PTZ	100	30
2	1.48	MES	300	30
		PTZ	30	70
3	2.29	MES	100	100
		PTZ	100	100
4	0.48	MES	300	30
		PTZ	300	30
5	2.17	MES	300	100
		PTZ	300	100
6	1.61	MES	300	100
		PTZ	100	20
7	1.53	MES	300	100
		PTZ	100	100
8	1.45	MES	300	30
		PTZ	100	100
9	0.97	MES	100	30
		PTZ	100	100
10	1.28	MES	300	10
		PTZ	300	70
11	2.56	MES	300	100
		PTZ	300	40

Comparison substance	Test[3)]	Dose[4)]	Action[5)]
Carbamazepine	MES	100	100
	PTZ	100	0
Valproate	MES	100	0
	PTZ	100	30

Notes for Table 1:

1) For numbering of the compounds see working examples

2) Octanol/water partition coefficient

3) MES = maximum electroshock, PTZ = s.c. pentetrazole

4) in mg/kg

5) in % of the protected animals

The preparation of the novel compounds of the general formula **1** will be illustrated in greater detail with the aid of working examples.

Working Examples

General procedure for the preparation of the compounds of the formula **1** according to Table 1, Examples 1-11.

Variant A

0.05 mol of 1-arylimidazolin-2,4-dione of the general formula **2** (n=0) [lacuna] 200 mg of 4-toluenesulfonic acid [lacuna] added to 100 ml of an appropriate secondary amine. The mixture is then heated under reflux in a Soxhlet extractor, the extraction thimble previously being filled with about 25 g of a water-

binding solid (calc. sodium sulfate, magnesium sulfate, NaOH, KOH, zeolites are suitable). After a reaction time of 8 to 30 hours, the solution is filtered hot and distilled to approximately half the volume in a rotary evaporator. The clear solution is cooled in an ice bath and the crystal magma obtained is separated off from the amine. Starting substance contained in the crude product is extracted with 50 ml of hot acetone. The product is recrystallized from n-propanol.
About 0.02 mol of unreacted 1-arylimidazolin-2,4-dione can be recovered from the separated amine.

Variant B

0.05 mol of 1-aralkylimidazolin-2,4-dione of the general formula **2** (n=1) is reacted with a sec. amine as described under A. After a reaction time of 8 to 30 hours, the solution is filtered hot and then concentrated to dryness in a rotary evaporator. 50 ml of methylene chloride and 50 ml of 2N HCl are added to the residue. The organic phase is separated off and the aqueous phase is extracted a further two times with methylene chloride. The aqueous phase isolated is rendered alkaline with 50 ml of 10% strength NaOH and the 1-4-amino-1-aralkylimidazolin-2-one [sic] is extracted with 100 ml of methylene chloride. The ether extracts are dried over sodium sulfate. After distilling off the methylene chloride, the crude product is recrystallized from ethanol or acetone.

Variant C

0.05 mol of 1-ar(alk)ylimidazolin-2,4-dione of the general formula **2** is reacted with 100 ml of dimethylammonium dimethylcarbamate as described under A and B. After a reaction time of 40 hours, the mixture is worked up according to variant A or B.

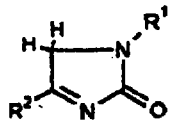
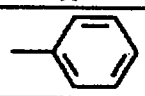
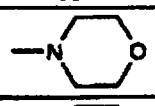
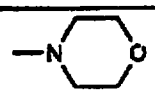
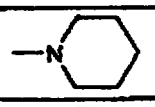
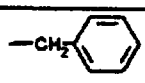
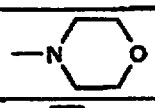
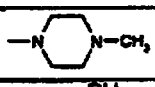
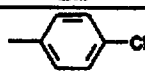
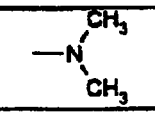
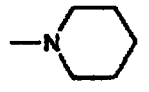
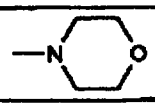
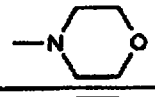
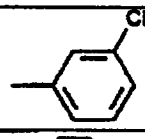
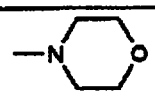
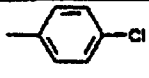
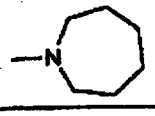


Table 2

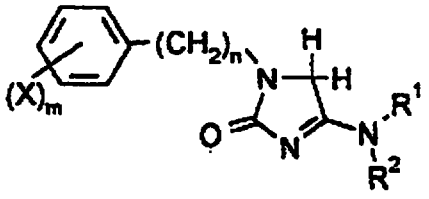
Example No.	R^1	R^2	Var.	Reaction time (h)	M.p. (°C)	Yield (%)
1			A	15	248	42 [1)]
2			A	15	266	75 [1)]
3			A	20	248	60 [1)]
4			B	15	158	48
5			A	12	254	68 [1)]
6			C	40	292	13
7			A	30	190	52 [1)]
8			A	15	268	65 [1)]
9			A	18	255	54 [1)]
10			B	30	237	27
11			A	8	216	88 [1)]

[1)] recovered starting material was taken into account when calculating the yield

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Patent Claims

1. Novel compounds of the general formula **1**



n = 0, 1
m = 0, 1, 2, 3, 4, 5

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in which

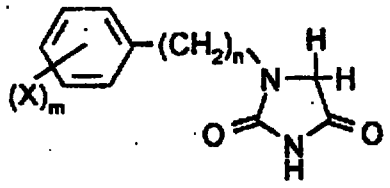
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl or halogen,
R^1 and R^2 = C_1-C_4-alkyl, cycloalkyl or heteroalkyl
or
R^1 and R^2 together are an alkylene group having 2-6 carbon atoms in which a $-CH_2-$ group can be replaced by oxygen, nitrogen or sulfur.

2. Compounds according to claim 1,

1-phenyl-4-morpholinoimidazolin-2-one
1-(4-methoxy)-4-piperidinoimidazolin-2-one
1-(4-chlorophenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-piperidinoimidazolin-2-one
1-(4-chlorophenyl)-4-dimethylaminoimidazolin-2-one
1-(4-bromophenyl)-4-morpholinoimidazolin-2-one
1-(3-chlorophenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-hexamethyleneiminoimidazolin-2-one
1-(4-chlorophenyl)-4-(4-methylpiperazino)imidazolin-2-one
1-(4-methylphenyl)-4-morpholinoimidazolin-2-one
1-(4-chlorophenyl)-4-(cyclohexylmethylamino)imidazolin-2-one
1-(4-fluorophenyl)-4-morpholinoimidazolin-2-one
1-benzyl-4-morpholinoimidazolin-2-one

* C L M S *

3. Process for the preparation of the compounds of the general formula **1**, characterized in that a [sic] compounds of the general formula **2**



n = 0, 1
m = 0, 1, 2, 3, 4, 5

in which
X = hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, trifluoromethyl or halogen

are reacted with a secondary amine HNR^1R^2 at temperatures between 50°C and 160°C, R^1 and R^2 having the meaning indicated.

4. Pharmaceutical preparations characterized in that, as active substance, they contain at least one compound of the general formula **1** and, if appropriate, pharmaceutical excipients and auxiliaries.

5. Pharmaceutical preparations according to claim 4 characterized in that, as active substance, they contain at least one of the compounds according to claim 2.

6. Use of the compounds of the general formula **1** for the production of medicaments for the treatment of epileptic disorders.

7. Use of the compounds according to claim 2 for the production of medicaments for the treatment of epileptic disorders.

* C L M S *